

PEPTIDES DERIVATIVES COMPRISING THIAZEPINE GROUP FOR THE TREATMENT OF
HYPERLIPIDEMIC CONDITIONS

This invention relates to benzothiazepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These benzothiazepines possess
5 ileal bile acid transport (IBAT) inhibitory activity and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions and they are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said benzothiazepine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit IBAT in a
10 warm-blooded animal, such as man.

It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for cardiovascular atherosclerotic disease (for instance "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman G., Carmena R. Cullen P. *et al*; Circulation
15 1999, 100, 1930-1938 and "Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals from the American Heart Association" Grundy S, Benjamin I., Burke G., *et al*; Circulation, 1999, 100, 1134-46). Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve, for instance, treatment with
20 HMG-CoA reductase inhibitors, preferably statins such as simvastatin and fluvastatin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol. One recently proposed therapy ("Bile Acids and Lipoprotein Metabolism: a Renaissance for Bile Acids in the Post Statin Era" Angelin B, Eriksson M, Rudling M; Current Opinion on Lipidology, 1999, 10, 269-74) involved the
25 treatment with substances with an IBAT inhibitory effect.

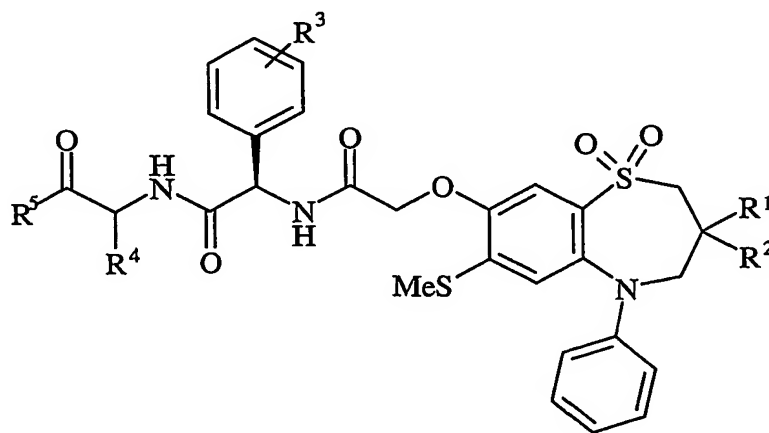
Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by the IBAT mechanism. Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia (see for instance "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties",
30 Biochemica et Biophysica Acta, 1210 (1994) 255- 287). Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions. Compounds possessing such IBAT inhibitory activity have been described, see for instance compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO

96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/50051, WO 03/020710, WO 03/022825,
 5 WO 03/022830, WO 03/022286 and EP 0 864 582.

A further aspect of this invention relates to the use of the compounds of the invention in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia,
 10 hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). In addition, these compounds are expected to be useful for the prevention and treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases,
 15 inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks.

The present invention is based on the discovery that certain benzothiazepine
 20 compounds surprisingly inhibit IBAT. Such properties are expected to be of value in the treatment of disease states associated with hyperlipidaemic conditions.

Accordingly, the present invention provides a compound of formula (I):



(I)

25 wherein:

R^1 and R^2 are independently selected from C_{1-4} alkyl;

R^3 is hydrogen, hydroxy or halo;

R^4 is C_{1-4} alkyl optionally substituted by hydroxy, methoxy and methylS(O)_a wherein a is 0-2

5 R^5 is hydroxy or HOC(O)CH(R^6)NH-;

R^6 is selected from hydrogen and C_{1-3} alkyl optionally substituted by hydroxy, methoxy and methylS(O)_a wherein a is 0-2;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; with the proviso that when R^1 and R^2 are both butyl, R^5 is hydroxy and R^4 is

10 methylthiomethyl, methylsulphinylmethyl, 2-methylthioethyl, hydroxymethyl, methoxymethyl; R^3 is not hydrogen; and with the proviso that when R^1 and R^2 are both butyl, R^5 is HOC(O)CH(R^6)NH-, R^6 is hydroxymethyl and R^4 is hydroxymethyl; R^3 is not hydrogen.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups. For example, " C_{1-4} alkyl" and C_{1-3} alkyl includes methyl, ethyl and propyl and
15 isopropyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals. The term "halo" refers to fluoro, chloro, bromo and iodo.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for
20 example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline
25 earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug
30 which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

10 An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups
15 for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

20 A suitable value for an *in vivo* hydrolysable amide of a compound of the formula (I) containing a carboxy group is, for example, a *N*-C₁₋₆alkyl or *N,N*-di-C₁₋₆alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention
25 encompasses all such optical, diastereoisomers and geometric isomers that possess IBAT inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess IBAT inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in
30 solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess IBAT inhibitory activity.

- 5 -

Specific values of R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R^1 and R^2 are both butyl.

5 One of R^1 and R^2 is ethyl and the other is butyl.

R^3 is hydrogen or hydroxy.

R^3 is hydrogen.

R^3 is 4-hydroxy.

10 R^4 is selected from C_{1-4} alkyl, hydroxymethyl, 1-hydroxyethyl, methoxymethyl, methylthiomethyl, methylsulphinylmethyl, mesylmethyl, 2-methylthioethyl, 2-methylsulphinylethyl and 2-mesylethyl.

R^4 is selected from methyl and ethyl.

R^5 is hydroxy.

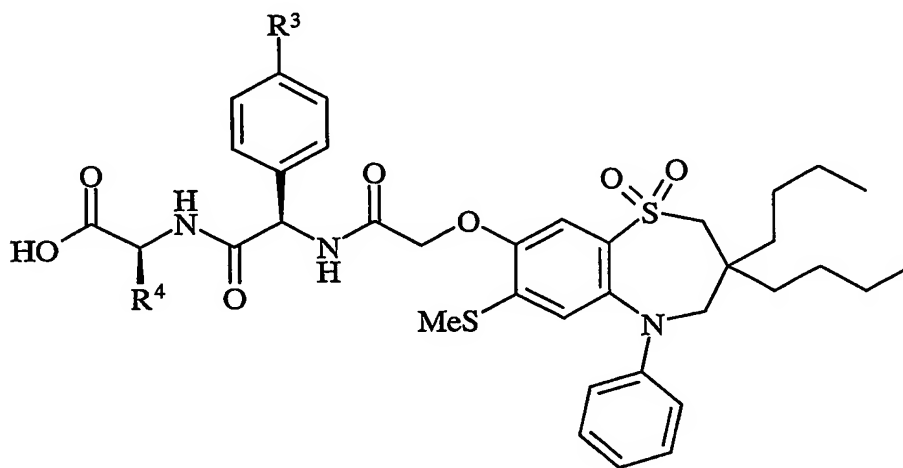
R^5 is $HOC(O)CH(R^6)NH-$.

15 R^6 is selected from hydrogen, methyl and hydroxymethyl.

The chiral centre at $(R^5C(O))C^*(R^4)(H)(NHC(O))$ is of the S configuration.

The chiral centre at $(R^5C(O))C^*(R^4)(H)(NHC(O))$ is of the R configuration.

In a further aspect of the invention there is provided a compound of formula (I) which is a compound of formula (I'):



(I')

wherein:

R^4 is selected from C_{1-4} alkyl, hydroxymethyl, 1-hydroxyethyl, methoxymethyl, methylthiomethyl, methylsulphinylmethyl, mesylmethyl, 2-methylthioethyl, 2-

25 methylsulphinylethyl and 2-mesylethyl and R^3 is hydroxy; or

R⁴ is selected from C₁₋₄alkyl, 1-hydroxyethyl, mesylmethyl, 2-methylsulphinyloethyl and 2-mesyloethyl and R³ is hydrogen;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Suitable compounds of the invention include:

- 5 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxyethyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxypropyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxybutyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 10 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-methylpropyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-methylbutyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 15 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-methylbutyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-hydroxypropyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 20 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-2-mesyloethyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-methylsulphonylpropyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 25 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxy-3-mesylpropyl) carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxyethyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 30 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-3-methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

10 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-methylsulphinylethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-mesyylethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

25 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-2-methoxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-3-methylthiopropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A further suitable compound of the invention is:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-((*S*)-1-carboxy-3-methylsulphinylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-

5 1,5-benzothiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

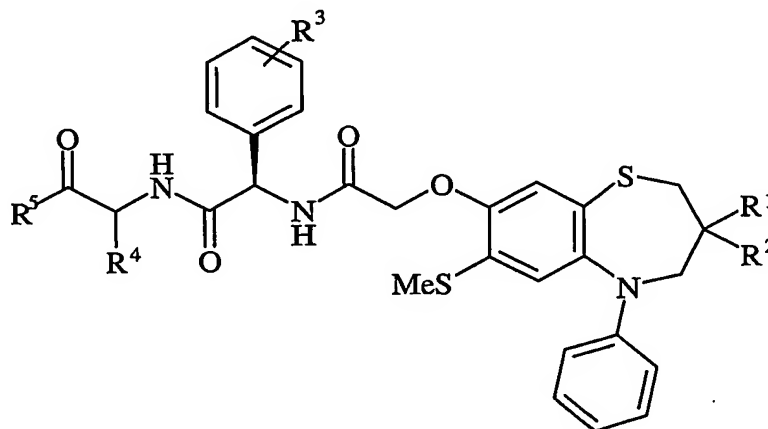
In another aspect of the invention, preferred compounds of the invention are any one of the examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

10 Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as

15 defined in formula (I)) comprises of:

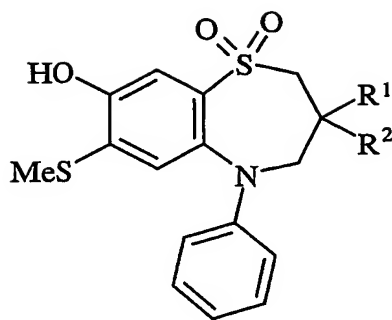
Process 1): oxidising a benzothiazepine of formula (II):



(II);

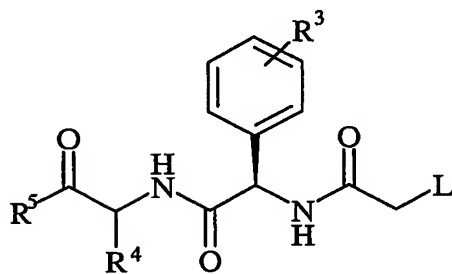
Process 2): reacting a compound of formula (III):

- 9 -



(III)

with a compound of formula (IV):

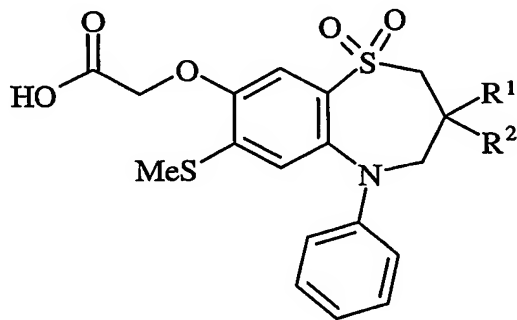


(IV)

5

wherein L is a displaceable group;

Process 3): reacting an acid of formula (V):

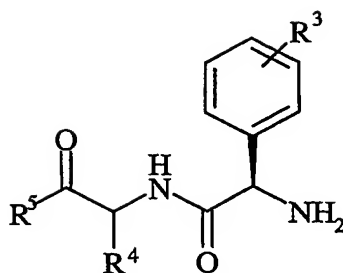


(V)

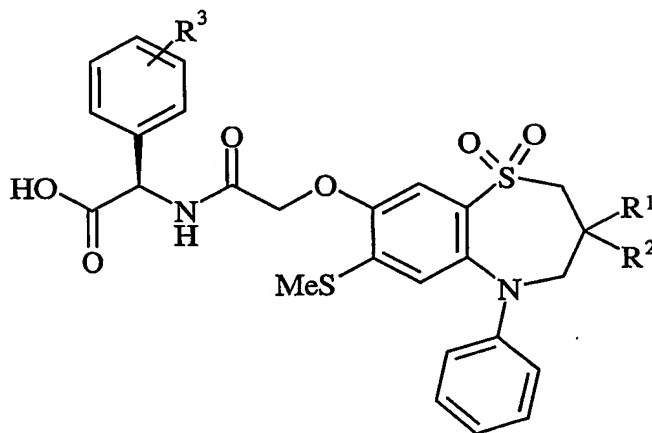
10

or an activated derivative thereof; with an amine of formula (VI):

- 10 -



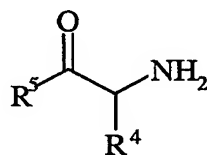
(VI);

Process 4): reacting an acid of formula (VII):

(VII)

5

or an activated derivative thereof; with an amine of formula (VIII):



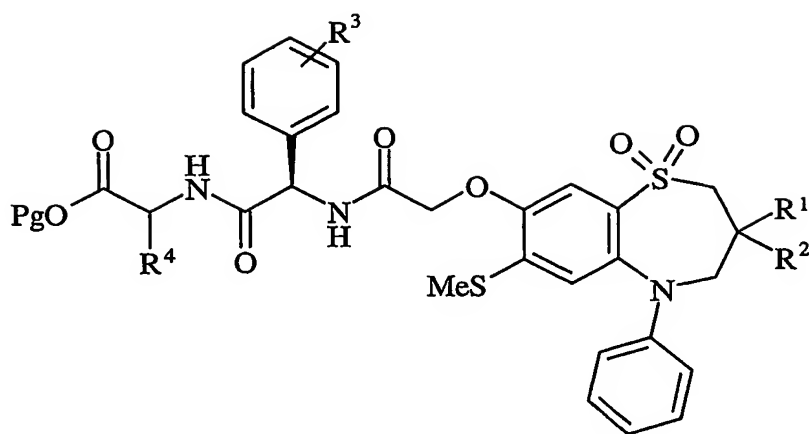
(VIII)

Process 5): for compounds of formula (I) wherein R⁵ is HOC(O)CH(R⁶)NH₂; reacting a10 compound of formula (I) wherein R⁵ is hydroxy with an amine of formula (IX):

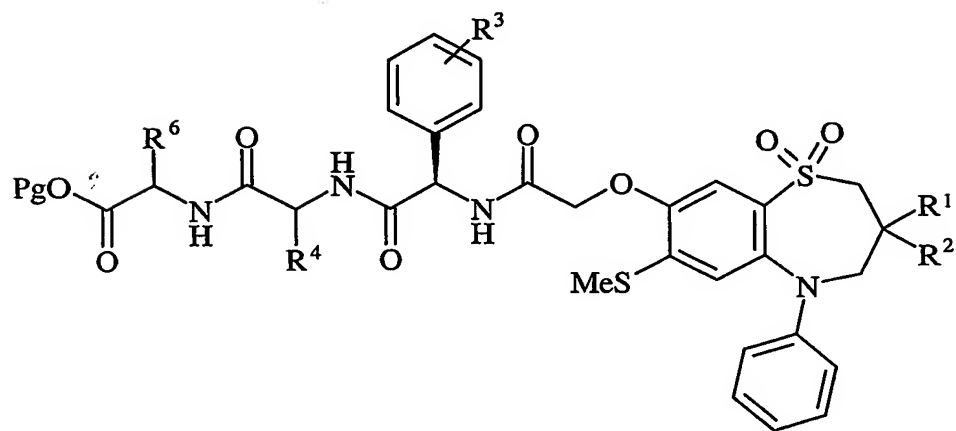
(IX)

Process 6): deprotecting a compound of formula (X) or a compound of formula (XI):

- 11 -



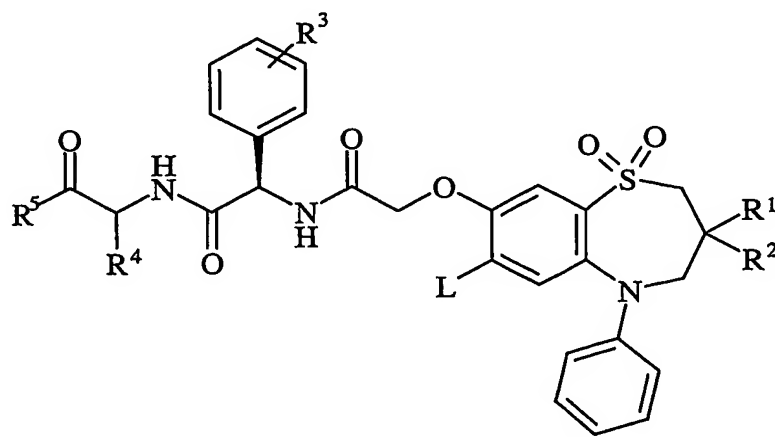
(X)



(XI)

5 wherein Pg is an acid protecting group;

Process 7) reacting a compound of formula (XII):



(XII)

wherein L is a displaceable group; with methylthiol;

and thereafter if necessary or desirable:

- i) converting a compound of the formula (I) into another compound of the formula (I);
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

5 L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

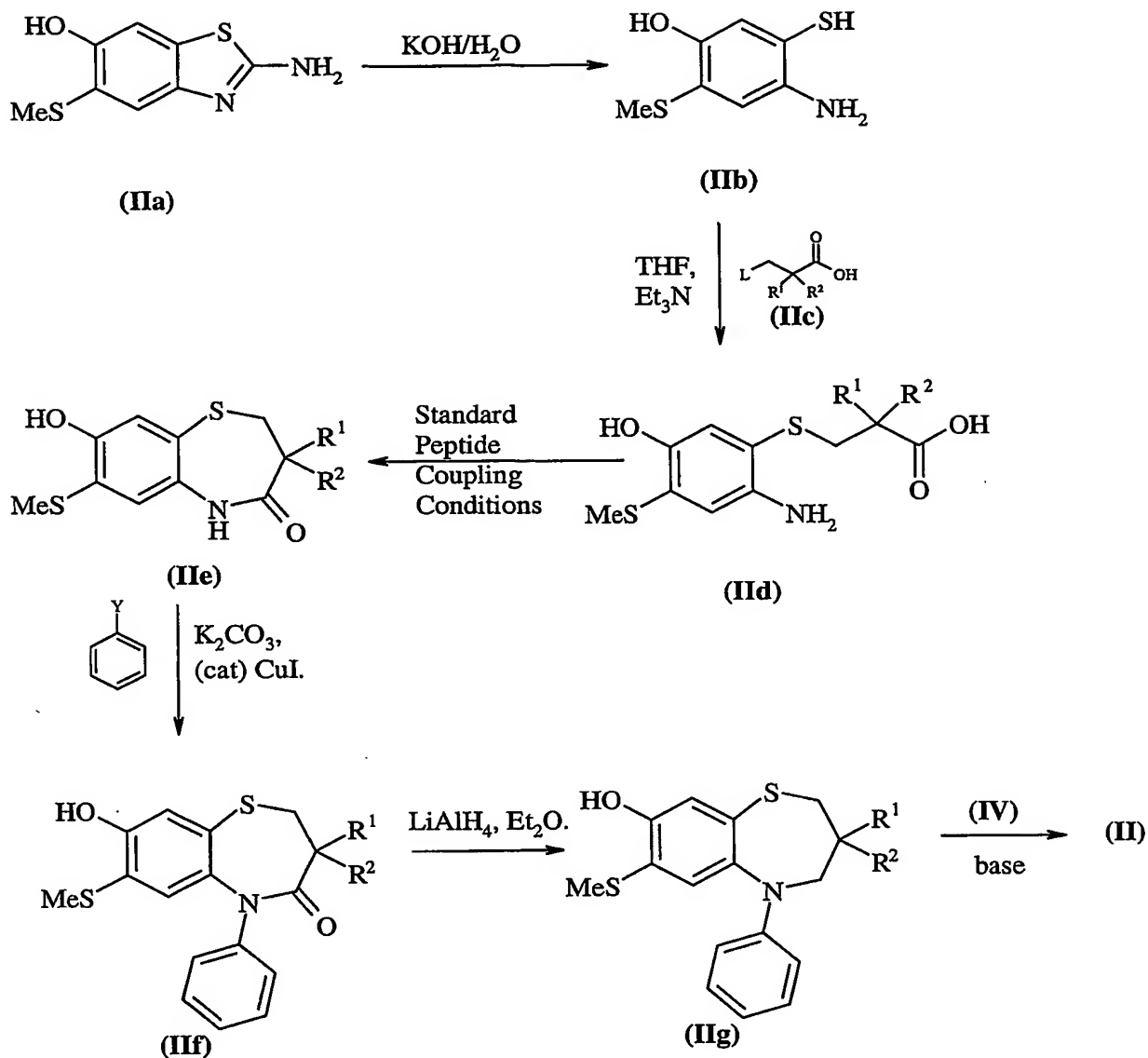
Pg is an acid protecting group, suitable values for Pg are given below as carboxy protecting groups. Preferably Pg is C₁₋₄alkyl.

10 Specific reaction conditions for the above reactions are as follows.

Process 1): Benzothiazepines of formula (II) may be oxidised under standard sulphur oxidation conditions; for example using hydrogen peroxide and trifluoroacetic acid at a temperature in the range of 0°C to reflux, preferably at or near room temperature.

Compounds of formula (II) may be prepared according to Scheme I.

- 13 -



Scheme 1

wherein L is a displaceable group as defined above, and Y is a displaceable group, for example halo.

- 5 Compounds of formula (IIa) and (IIc) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 2): Alcohols of formula (III) may be reacted with compounds of formula (IV) in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as MeCN,

- 10 dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

Compounds of formula (III) may be prepared by oxidising a compound of formula (IIg) using the conditions outlined in *Process 1*).

Compounds of formula (IV) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

5 *Process 3*), *Process 4* and *Process 5*): Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for
10 example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and DMF. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides,
15 and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

20 Compounds of formula (V) or (VII) may be prepared according to Scheme 1 using the appropriate replacement for the compound of formula (IV).

Amines of formula (VI), (VIII) and (IX) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 6): Protected acids of formula (IX) or (XI) may be deprotected under standard
25 conditions such as those described below.

Protected acids of formula (X) or (XI) may be prepared by any of the procedures above with the appropriate modifications.

Process 7): Compounds of formula (XII) may be reacted with methylthiol in the presence of base, for example an inorganic base such as sodium carbonate or an organic base such as
30 Hunigs base, in the presence of a suitable solvent such as DMF or THF at a temperature in the range of 0°C to reflux.

Compounds of formula (XII) may be prepared by any of the procedures above with the appropriate modifications.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an

arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by
5 treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl
10 group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group,
15 for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

20 The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possess IBAT inhibitory activity. These properties may be assessed, for example, using an *in vitro* test assay for studying the effect on bile acid uptake in IBAT-transfected cells (Smith L., Price-Jones M.
25 J., Hugnes K. T. and Jones N. R. A.; J Biomolecular Screening, 3, 227-230) or *in vivo* by studying the effect on radiolabelled bile acid absorption in mice/rats (Lewis M. C., Brieady L. E. and Root C., J., J Lip Res 1995, 36, 1098-1105).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable
30 salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular,

intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

- 5 The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg or 0.01-50 mg/kg, and this normally provides a therapeutically-effective dose. In another aspect of the invention the compound of formula (I),
10 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 0.001- 20 mg /kg or 0.1 - 200 mg /day, particularly 1 -20 mg/day to provide a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. In
15 another aspect a daily dose in the rage of 0.02-20 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

- According to a further aspect of the present invention there is provided a compound of
20 the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

- We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are
25 effective IBAT inhibitors, and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

- 30 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

5 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia
10 (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a
15 prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves,
20 vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound
25 of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

30 According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a

compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need
5 of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating dyslipidemic conditions and disorders such as hyperlipidaemia,
10 hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate,
15 solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina
20 pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in need of such treatment which comprises administering to
25 said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a
30 warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

There is evidence that an IBAT inhibitor might potentially be useful in the treatment and/or prevention of gallstones. According to a further feature of this aspect of the invention there is provided a method of treating and / or preventing gallstones in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal
5 an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

The size of the dose required for the therapeutic or prophylactic treatment will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg,
10 preferably 1-50 mg/kg is envisaged.

The IBAT inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. According to this
15 aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore and an additional IBAT inhibitory substance as defined hereinbefore and an additional hypolipidaemic agent for the conjoint treatment of hyperlipidaemia.

20 In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable HMG Co-A reductase inhibitors, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are
25 statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a
30 pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A further particular statin is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate,

solvate of such a salt or a prodrug thereof. A preferable particular statin is rosuvastatin calcium salt.

In an additional aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may be administered in association with an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and/or a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

An HMG CoA-reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof will by its action decrease the endogenous cholesterol available for the bile acid synthesis and have an additive effect in combination with the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof on lipid lowering.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyramine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesterolaemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a
5 prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of
10 treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate,
15 solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a
20 prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound
25 of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

30 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase

inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable
5 salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase
10 inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate
15 of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate
of such a salt or a prodrug thereof, and a bile acid binder.

20 According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder.

25 According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate
30 of such a salt or a prodrug thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a bile acid binder; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

5 According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate
10 of such a salt or a prodrug thereof; in a second unit dosage form;
- c) a bile acid binder; in a third unit dosage form; and
- d) container means for containing said first, second and third dosage forms.

 According to a further aspect of the present invention there is provided a kit comprising:

- 15 a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- 20 c) container means for containing said first and second dosage forms.

 According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a
25 first unit dosage form;
- b) a bile acid binder, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

 According to a further aspect of the present invention there is provided a kit comprising:

- 30 a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) a bile acid binder; in a third unit dosage form; and
- d) container means for containing said first, second and third dosage forms.

5 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

10 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

 According to another feature of the invention there is provided the use of a compound
15 of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

20 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

25 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a bile acid binder, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

 According to another feature of the invention there is provided the use of a compound
30 of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture

of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable excipient, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;
- a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;
- a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;
- a fibric acid derivative; for example clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate;
- a nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and niceritrol;
- a phytosterol compound for example stanols;
- probucol;
- an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);
- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;
- insulin;
- sulphonylureas including glibenclamide, tolbutamide;
- metformin; and/or
- acarbose;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril

sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphan-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, 5 quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and 10 ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin 15 II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, 20 solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular 25 the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. 30 Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof. Additional suitable PPAR alpha and/or gamma agonists are NN622/Ragaglitazar and BMS 298585.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- 5 c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament
10 for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for
15 use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to
20 a warm-blooded animal, such as man in need of such therapeutic treatment.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of IBAT in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.
30

Many of the intermediates described herein are novel and are thus provided as a further feature of the invention. For example compounds of formula (X) and (XI) show IBAT

inhibitory activity when tested in the above referenced *in vitro* test assay and are thus claimed as a further feature of the invention.

Thus in a further feature of the invention, there is provided a compound of formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

According to an additional aspect of the present invention there is provided a compound of the formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

Thus according to this aspect of the invention there is provided a compound of the formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a

compound of formula (X) or (XI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the
5 invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:

- 10 (i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;
- 15 (iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 µm (Merck);
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic
20 resonance chemical shift values were measured in deuterated CDCl₃ (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer unless otherwise stated data was recorded at 400 MHz; and peak multiplicities are shown as follows:
- 25 s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; ABq, AB quartet; ABd, AB doublet, ABdd, AB doublet of doublets; dABq, doublet of AB quartets; LCMS were recorded on a Waters ZMD, LC column xTerra MS C₈(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-
30 detector diode array equipped; unless otherwise stated the mass ion quoted is (MH⁺); unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Cromasil C₈, 7 µm,

(Akzo Nobel); MeCN and de-ionised water 10 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

5 (viii) where solutions were dried sodium sulphate was the drying agent;

(ix) the following abbreviations may be used hereinbefore or hereinafter:-

DCM dichloromethane;

DMF *N,N*-dimethylformamide;

TBTU O-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate;

10 EtOAc ethyl acetate;

MeCN acetonitrile;

DIPEA di-isopropylethylamine; and

THF tetrahydrofuran.

15 Example 1

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-(*S*)-1-carboxypropyl]carbamoyl}-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 2 WO02/50051; 50 mg, 0.076 mmol), *tert*-butyl (2*S*)-2-aminobutanoate hydrochloride (20 mg, 0.102 mmol) and *N*-methylmorpholine were dissolved in DCM (1.0 ml). The mixture was stirred for 5 min at room temperature. TBTU (30 mg, 0.093 mmol) was added and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue
25 was dissolved in concentrated formic acid (1.0 ml). The mixture was heated to 50°C and kept for 2 hours at this temperature. The reaction mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent. 30 mg (53%) of the title compound was obtained. NMR (DMSO-*d*₆): 0.6-0.8 (m, 9H), 0.9-1.7 (m, 14H), 2.16 (s, 3H), 3.2-3.4 (m, 2H), 3.6-3.8 (brs, 2H), 4.0-4.1 (m,
30 1H), 4.75 (q (AB), 2H), 5.51 (d, 1H), 6.65-7.30 (m, 11H), 8.41 (d, 1H), 8.50 (d, 1H), 9.3-9.4 (brs, 1H).

Example 2

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -{N'-[(S)-1-ethoxycarbonyl]ethyl}carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 4; 0.042 g, 0.057 mmol) in EtOH (6 ml, 95 %) was added a solution of NaOH (0.153 g, 0.250 mmol) in water (0.3 ml) and the mixture was stirred for 1 hour. The reaction was quenched with AcOH (0.04ml), concentrated and partitioned between EtOAc and water. The organic phase was concentrated and the residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The desired compound was obtained in 0.024 g (59 %) as a white solid. NMR (CD₃OD): 0.70-0.90 (6H, m), 1.00-1.60 (15H, m), 2.10 (3H, s), 3.25 (2H, s), 3.75 (2H, brs), 4.25-4.40 (1H, m), 4.60-4.80 (2H, m), 5.60 (1H, d), 6.70 (1H, s), 6.90-7.50 (11H, m).

15 Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

A solution of NaOH (4.67 g, 116 mmol) in water (10 ml) was added to a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonyl-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 2; 15.45 g, 28.71 mmol) in EtOH (160 ml). The solution was stirred for 30 min at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 1.0 M HCl. The aqueous layer was extracted twice more with EtOAc and the combined organic extracts were washed with brine and concentrated to give the title compound (14.28 g, 98 %) as a white powder. NMR (500 MHz, DMSO-d₆) 0.65-0.80 (m, 6H), 0.90-1.50 (m, 12H), 2.20 (s, 3H), 3.25 (s, 2H), 3.65 (brs, 2H), 4.80 (s, 2H), 6.70 (s, 1H), 6.80-7.30 (m, 6H), 13.20 (s, 1H).

Method 2**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonyl-2,3,4,5-tetrahydro-1,5-benzothiazepine**

To a suspension of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 3; 12.85 g, 28.71 mmol) in MeCN (150 ml) was added ethyl bromoacetate (3.85 ml, 34.6 mmol), tetrabutylammonium bromide (0.925 g, 2.869 mmol) and sodium carbonate (12.85 g, 121.2 mmol). The mixture was heated under reflux for 5 hours. The solvent was removed under reduced pressure and the residue was partitioned between DCM and 0.5 M HCl. The organic layer was washed with brine, dried (MgSO₄) and concentrated. Chromatography using DCM/EtOAc (9:1) as eluent gave the desired product (15.45 g) as a tan oil. NMR 0.70-0.85 (m, 6H), 1.00-1.55 (m, 15H), 2.15 (s, 3H), 3.10 (s, 2H), 3.70 (brs, 2H), 4.25 (q, 2H), 4.70 (s, 2H), 6.65 (s, 1H), 6.90-7.30 (m, 6H).

Method 3**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine**

To 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (synthesised by the of WO9616051 for the corresponding 3-butyl-3-ethyl analogue; 40 mg, 0.08 mmol) was added DMF (2 ml), sodium methanethiolate (60 mg, 0.85 mmol) and sodium borohydride (60 mg, 1.6 mmol). The reaction was run overnight at 60°C. Additional sodium borohydride (60 mg, 1.6 mmol) and sodium methanethiolate (60 mg, 0.85 mmol) was added and the temperature was raised to 120°C. The reaction heated at this temperature for 4 hours and then cooled to room temperature. Then acetic acid was added under a flow of nitrogen, through sodium hypochlorite overnight. Water and EtOAc was added and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with HCl (1M), dried and concentrated under reduced pressure. The residue was then purified by flash chromatography [EtOAc : heptane, 1:4] to give the title compound 0.34 g (93%). NMR 0.7-0.9 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.1 (s, 2H), 3.4 (s, 2H), 3.7 (brs, 2H), 6.7 (s, 1H), 6.85-7.05 (m, 2H), 7.2-7.4 (m, 2H).

Method 4**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -{N'-[(S)-1-(ethoxycarbonyl)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine**

A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 5; 0.050 g, 0.078 mmol), L-alanine, ethyl ester, hydrochloride (0.012 g, 0.078 mmol) and N-methylmorpholine (0.030 ml, 0.272 mmol) in DCM (4 ml) was stirred at ambient temperature for 10 min after which TBTU (0.033 g, 0.103 mmol) was added. After additional 2h the reaction mixture was transferred to a separator funnel and washed with water and brine, dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography on silica gel (Hept:EtOAc-1:1), to give 0.048 g (83 %) of the desired product as a white solid. NMR 0.70-0.85 (6H, m), 1.00-1.55 (18H, m), 2.10 (3H, s), 3.15 (2H, s), 3.70 (2H, brs), 4.05-4.25 (2H, m), 4.50-4.70 (2H, m), 5.50-5.65 (1H, m), 6.30-6.45 (1H, m), 6.65 (1H, s), 6.95-7.10 (3H, m), 7.20-7.50 (8H, m), 8.05 (1H, d).

15

Method 5**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine**

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 6; 300 mg, 0.46 mmol) was dissolved in methanol (5 ml). NaOH (100 mg in 0.2 ml water) was added to the solution and the mixture was stirred at room temperature for 1 hour. Acetic acid (0.3 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The DCM layer was separated, dried and evaporated under reduced pressure to give the title compound 270 mg (92%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 (brs, 2H), 3.6-3.8 (m, 2H), 4.6 (s, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.8 (d, 1H).

25

Method 6**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine**

- 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-
5 1,5-benzothiazepine (Method 1; 250 mg, 0.49 mmol), (R)-2-phenylglycine methyl ester hydrochloride (120 mg, 0.60 mmol) and DIPEA (300 mg, 2.3 mmol) were dissolved in DCM (10 ml) and the mixture was stirred for 5 min in room temperature. TBTU (210 mg, 0.65 mmol) was added and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was placed on a column and the
10 product was eluted with DCM/EtOAc (90:10) to give the title compound 306 mg (95%).
NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 brs, 2H), 3.6-3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.9 (d, 1H).